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PSYCHIATRIC COMORBIDITY, RESTLESS LEGS SYNDROME AND NOCTURNAL EATING DISORDER: A CASE-CONTROL STUDY

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INTRODUCTION

1. Restless Legs Syndrome: Clinical Features, Diagnosis and Pathophysiology.

Restless legs syndrome (RLS) is a somatosensory disorder that is clinically diagnosed according to the four main criteria established by the International Restless Legs Syndrome Study Group (IRLSSG) (*Walters AS, 1995*), and reviewed in 2003 (*Allen RP et al, 2003*): an urge to move the legs, usually associated with unpleasant leg sensations; induction or exacerbation of symptoms by rest; symptom relief on activity; diurnal fluctuations in symptoms with worsening in the evening and at night. The three supportive criteria include periodic limb movements (PLM), therapeutic response to dopaminergic (DAergic) agents, and a family history of the disorder. The most important associated feature is sleep disturbance. The second common finding is a progressive course. The third finding is the absence of clear-cut signs of other neurological diseases in patients with idiopathic RLS (**Figure 1).**

As well as the sensory features, patients may experience motor features, in addition to the voluntary movements they make to alleviate discomfort. These involuntary movements may arise in sleep or while awake, and typically involve brief repetitive movements of the legs, ranging from subtle extension of the hallux to flexion of the hip, knee, and ankle. About 80% of patients with the syndrome experience these movements labelled periodic limb movements in sleep (PLMS) and wakefulness (PLMW). These movements can result in arousals, leading to unrefreshing sleep and sleep maintenance insomnia (*Trenkwalder C et al, 2005; Allen RP et al, 2003; Leschziner G and Gringras P, 2012*).

RLS prevalence in the general population is 10–12% (with a range of 5–20% in different studies), increasing with age and among women (*Trenkwalder C et al, 2005; Allen RP et al, 2003*).

RLS may be idiopathic or symptomatic. Idiopathic disease seems to have a strong genetic component, with a family history in 18.5-60% of patients (*Rangarajan S et al, 2007; Vogl FD et al, 2006*). RLS has been associated

with a wide variety of conditions, most often iron deficiency and uraemia. Other disease associations include cardiovascular disease, obesity, diabetes, rheumatological disorders, peripheral neuropathy, radiculopathy, Parkinson's disease, multiple sclerosis, Charcot-Marie-Tooth disease, and spinal cord lesions. However, many of these diseases were not seen in all studies, and the strengths of these associations are unclear (*Bassetti C et al, 2001; Trenkwalder C et al, 2005*; *Leschziner G and Gringras P, 2012*).

The diagnostic process requires special attention to exclude other conditions that may resemble RLS, so-called "RLS mimics", which include akathisia, nocturnal leg cramps, peripheral neuropathy, lumbosacral radiculopathy, painful legs and moving toes, growing pains, and attention deficit hyperactivity disorder (*Hening WA et al, 2009*).

A useful diagnostic tool is the suggested immobilization test, that evaluates periodic leg movements (PLM) and self-reported sensory symptoms for people who are instructed to remain still for 1 h while sitting on a bed with their legs outstretched (*Michaud M et al, 2002*). Polysomnography allows accurate assessment of PLMS, scoring them only if they occur in a series of four consecutive movements lasting 0.5-5 s, have an amplitude of one quarter or more of the toe dorsiflexion during calibration and are separated by intervals of 4-90 s. PLMS occur during stages 1-2 of NREM sleep, diminish during stages 3-4 and nearly always disappear during REM sleep. An index (number of PLMS per hour of sleep) greater than 5 for the entire night is considered pathologic and is supportive, although not specific, of the diagnosis of RLS (*Zucconi M et al, 2006*).

Since RLS is primarily a subjective disorder, a subjective scale of RLS symptoms represents the optimal instrument to measure disease severity for clinical assessment, research or therapeutic trials. In 2003, the IRLSSG proposed and validated a rating scale, consists of ten questions, whose total score progresses from 0 to 40 with the degree of disease severity (*Walters AS et al, 2003*).

The pathophysiology of RLS is poorly understood. Many regions of the nervous system from the periphery to the cortex contain structures involved

in somatosensory perception and in the generation of movement (*Trenkwalder C and Paulus W, 2010*). Electrophysiological studies suggest that PLM are involuntary and are organized at the brainstem or spinal level (*Trenkwalder C et al, 1996*). Patients with PLMS, with or without associated RLS, may have abnormal blink reflexes (*Briellmann RS et al, 1996*). H-reflexes and H-reflex modulation modulation (*Martinelli P and Coccagna G, 1976; Rijsman RM et al, 2005; Scaglione C et al, 2008*) and flexor reflex (*Bara-Jimenez W et al, 2000*) are impaired suggesting a brainstem or more rostral dysfunction leading to enhanced spinal excitability. Transcranial magnetic stimulation (TMS) studies have shown abnormal motor cortex excitability in RLS, which is reversible by dopamine agonist administration (*Nardone R et al, 2006; Kutukcu Y et al, 2006; Gorsler A and Liepert J, 2007; Rizzo V et al, 2009*).

Functional MRI (fMRI) studies in RLS patients demonstrated an activation of the thalamus (legs discomfort), cerebellum (legs discomfort and PLM), red nuclei and brainstem (PLM) (*Bucher SF et al, 1997*), and using only a motor paradigm, of the thalamus, putamen, middle frontal gyrus and cingulate gyrus (*Astrakas LG et al, 2008*). Recently, activation of the striatofrontolimbic area during night-time episodes of sensory leg discomfort and PLMs was reported and claimed to represent the neurofunctional substrate mediating the repetitive compulsive movements seen in RLS (*Margariti PN et al, 2012*). The hypothesis that dysfunction of the limbic system plays a role in the pathophysiology of idiopathic restless legs syndrome was also supported by a proton magnetic resonance spectroscopy study by Rizzo et al showing an abnormal medial thalamus metabolism in idiopathic RLS patients (*Rizzo G et al, 2012*).

MR studies using advanced techniques such as voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) looked for structural brain abnormalities in idiopathic RLS patients but reported contrasting results. Some studies disclosed regional brain changes, but affected brain structures differed in some studies (*Etgen T et al, 2005*; *Unrath A et al, 2007; Hornyak M et al, 2007*; *Connor JR et al, 2011*; *Unrath A et al, 2008*), while others

yielded no specific brain alterations (*Celle S et al, 2010; Comley RA et al, 2012; Rizzo G et al,* 2012) supporting the role of functional or metabolic impairment in RLS.

All these studies are consistent with a subcortical dysfunction. Therefore, RLS appears to be a complex movement disorder affecting several levels of the neuraxis, although the precise anatomic location of this dysfunction remains unsettled *(Barrière G et al, 2005*). However, there is evidence for impairment of sensorimotor processing at the level of the cortex and the spinal cord, suggesting altered subcortical/supraspinal control.

Iron deficiency seems to be implicated in RLS pathophysiology. Although iron deficiency alone is not sufficient to cause restless legs syndrome—and neither is it necessary—precipitation or exacerbation of symptoms with venesection is well described, and serum ferritin correlates inversely with symptom severity (*Tobiasson M et al, 2010*). Magnetic resonance imaging and cerebrospinal fluid studies and autopsy specimens of substantia nigra have shown that brain iron stores are reduced in patients with RLS (*Earley CJ et al, 2000; Connor JR et al, 2003*). Iron is an essential cofactor for tyrosine hydroxylase (the rate-limiting enzyme in dopamine synthesis) and seems to play a crucial role in dopamine metabolism (*Allen RP, 2004*).

Dopaminergic system involvement is highly probable because effective treatment with dopamine agonists has been confirmed by controlled trials, whereas dopamine antagonists worsen symptoms or may even elicit RLS (*Barrière G et al, 2005*). However, it is unclear whether the dopaminergic system is hypo- or hyperactive in RLS. PET and SPECT studies revealed controversial results on the pre- and post-synaptic dopaminergic neurotransmission system. Almost all have focused on the striatum, a brain region receiving dense dopaminergic innervations, showing slightly reduced binding or no difference of both presynaptic ([^{123}I]βCIT, [^{123}I]IPT or [^{99m}Tc]TRODAT-1 in SPECT studies and ^{18}F-dopa in PET studies) and postsynaptic D2 radioligand ([^{123}I]IBZM in SPECT studies and ^{11}C-raclopride in PET studies) in RLS patients compared with control subjects (*Wetter TC et al, 2004; Hilker R et al, 2006*). Taken together, these results

suggest that at nigrostriatal pathway level the membrane dopamine transporter and postsynaptic D2-receptor seem to be either unchanged or mildly reduced in patients with idiopathic RLS. In addition to ^{11}C-raclopride in striatal regions, another PET study investigated other extrastriatal dopaminergic regions by FLB 457 (a new postsynaptic high-affinity D2 radioligand) disclosing a higher binding potential in patients than controls in the limbic and associative part of the striatum, medial and posterior part of thalamus, anterior cingulate cortex and insula, all belonging to the medial nociceptive system which is thought to regulate the affective-motivational component of pain. The authors sustained the hypothesis of hypoactive dopaminergic neurotransmission associated with receptor up-regulations (*Cervenka S et al, 2006*). An involvement of the medial nociceptive system was supported also by a PET study with [^{11}C]diprenorphine, a non-selective opioid receptor radioligand, which found regional negative correlations between ligand binding and RLS severity in areas serving the medial pain system (medial thalamus, amygdala, caudate nucleus, anterior cingulate gyrus, insular cortex and orbitofrontal cortex) (*von Spiczak S et al, 2005*).

A recent PET study in RLS showed lower dopamine-2 receptor (D2R) binding potentials (BP) in putamen and caudate, interpreted as an increase in synaptic DA (*Earley CJ et al, 2013*). Several lines of investigation suggest the pre-synaptic DAergic activity may be increased in RLS and thus could result in an increase in synaptic DA. CSF analysis in RLS disclosed an increase in 3-O-methyldopa (*Earley CJ et al, 2006; Allen et al, 2008*), found as a by-product of COMT metabolism of L-DOPA when the latter is in excess (*Cooper JR et al, 2003*). One interpretation of the CSF results is that they represented an increase in tyrosine hydroxylase (TH) activity and L-DOPA production (*Earley CJ et al, 2006*). This is supported by the finding of increased total TH, and in the more enzymatic active form, phosphorylated TH, in the autopsy brains of RLS patients (*Connor JR et al, 2009*).

Regarding dopaminergic structures beneath the basal ganglia, several studies have focused on the role of the dorso-posterior hypothalamic

dopaminergic A11 cell group in RLS, particularly under conditions of iron deprivation (*Qu S et al, 2007*). The A11 cell group represents the largest and possibly the only source of spinal DA, and its spinal projections modulate sensory inputs and sympathetic drive, predominantly with inhibitory action through D2 and especially D3 receptors (*Clemens S et al, 2006*). This theory was supported by animal models showing that D3 receptor knockout (D3KO) mice were hyperactive and manifested an increased wakefulness across the rest-activity cycle (*Accili D et al, 1996; Hue GE et al, 2003*) and that locomotor activities were significantly increased in A11-lesioned mice compared with controls (*Ondo WG et al, 2000; Qu S et al, 2007*).

In summary, even if cerebral metabolism in RLS probably reflects a dysfunction of the central dopaminergic system, it remains to be determined whether these alterations affect mainly the nigrostriatal and/or other central dopaminergic systems like the diencephalospinal or mesolimbic pathway and whether they are the primary mechanisms or only secondary phenomena within the manifestation of RLS symptoms.

2. Nocturnal Eating Disorders: Sleep-Related Eating Disorder and Night Eating Syndrome.

Night-time in humans is typically characterized by a prolonged period of fasting associated with sleep. Abnormal eating during the main sleep period has been categorized as either sleep-related eating disorder (SRED) or night eating syndrome (NES). According to the revised International Classification of Sleep Disorders (ICSD-2), SRED is a parasomnia consisting of ‘‘recurrent episodes of involuntary (out of control) eating and drinking during arousal from sleep with problematic consequences” (*American Academy of Sleep Medicine. The International Classification of Sleep Disorders, 2nd ed: Diagnostic and coding manual. Westchester, IL: American Academy of Sleep Medicine; 2005*) (**Figure 2**) such as consumption of peculiar combinations of food or high calorie foods, bizarre and toxic substances (frozen food, uncooked spaghetti, cat food, egg shells, coffee grounds, sunflower shells, buttered cigarettes, glue, and cleaning

solutions), morning anorexia, dangerous food preparation behaviour, sleep-related injury and weight gain (*Howell MJ et al, 2008*). Often, patients cannot be easily awakened and the eating is poorly recalled, thus SRED resembles sleep-walking.

The majority (60-83%) of reported cases of SRED are female (*Winkelman JW, 1998*) with a chronic course of the disorder (*Schenck CH et al, 1991).*

Polysomnography (PSG) has been used to characterize SRED. Most commonly, eating behaviour arises from NREM sleep and the majority of patients demonstrated excessive periodic limb movements in sleep (PLMS) (>5/h) and rhythmic masticatory muscle activity (RMMA) (*Vetrugno R et al, 2006*).

An associated primary sleep disorder, particularly sleep-walking and RLS, was identified in 68% and 13% of SRED patients, respectively *(Schenck CH et al, 1993).* Furthermore, SRED has been associated with psychotropic medications, in particular the benzodiazepine receptor agonist zolpidem, tricyclic antidepressants, anticholinergics, lithium, triazolam, olanzapine, and risperidone (*Morgenthaler TI and Silber MH, 2002; Schenck CH and Mahowald MW, 1994*).

The pathophysiology of SRED in unclear. SRED could be construed as a disorder whereby sleep-related motor and autonomic arousal processes happen to stimulate the appetitive-feeding pathways and elicit a time-inappropriate compulsive feeding behaviour (*Vetrugno R et al, 2006*). The beneficial effects of dopaminergic agents, an association with increased motor activity (rhythmic masticatory-muscle activity/RMMA, PLMS, RLS) suggestive of a generalized motor disinhibition probably of dopaminergic origin, and compulsive food-seeking episodes (dysfunction of dopaminergic system at the mesolimbic level) could suggest a pathogenic role for the dopaminergic system in nocturnal eating disorders (*Vetrugno R et al, 2006*).

NES is the other category of night-time eating. NES has no entry in the ICSD-2 classification, but diagnostic criteria for NES, different from the ICSD-2 criteria for SRED, have been proposed (*Birketvedt GS et al, 1999).*

NES could be considered an abnormality in the circadian rhythm of meal timing with a normal circadian timing of sleep onset. The disorder was thought to be a response to stress, and was originally studied among obese persons refractory to standard weight loss treatment (*Howell MJ et al, 2008*). For a diagnosis of NES all of Birketvedt et al's criteria must be met, i.e. evening hyperphagia, nocturnal awakenings, nocturnal hyperphagia, morning anorexia, absence of other eating disorders behaviour (*Birketvedt GS et al, 1999*). Recently Birketvedt et al's criteria were reviewed. The core criterion for NES is an abnormally increased food intake in the evening and night-time, manifested by (1) consumption of at least 25% of intake after the evening meal, and/or (2) nocturnal awakenings with ingestions at least twice per week. Awareness of the eating episodes is required, as is distress or impairment in functioning. Three of the following core features must also be endorsed: (1) morning anorexia, (2) a strong desire or urge to eat between dinner and sleep initiation and/or upon awakening at night from sleep, (3) sleep onset and maintenance insomnia, (4) the belief that one must eat in order to get to sleep, and (5) depressed mood or lowering of mood in the evening and night-time. These criteria must be met for a minimum duration of three months. The absence of other medical and/or psychiatric disorder was also required (*Allison CK et al, 2010*) (**Figure 3**).

Different studies have indicated a prevalence of NES of approximately 1.5% in adult populations (*Striegel-Moore RH et al, 2005).*

The relationship of SRED with NES is still unclear (*Vinai P et al, 2012*). SRED and NES share some overlapping features (nocturnal awakenings to eat with loss of control over consumption, sleep fragmentation and morning anorexia). Evening hyperphagia and sleep onset insomnia are typical of NES but not of SRED. Some authors have also considered impaired consciousness and subsequent amnesia for the eating episodes to be the major feature differentiating SRED from NES (*Winkelman JW, 1998; Vetrugno R et al, 2006; Provini F et al, 2009*). However, the level of consciousness during eating episodes in SRED may vary among episodes within the same night and from night-to-night over the longitudinal course

of the disorder (*Winkelman JW, 2006*). There is also a strong association between a diminished level of awareness and a history of sleepwalking and medications or substance use/abuse (*Vetrugno R et al, 2006*). Difficulties with the classification of SRED on the basis of impaired consciousness during the eating episodes are also highlighted in the revised International Classification of Sleep Disorders-2, which acknowledges that eating episodes in SRED may be accompanied by either clear or clouded consciousness. "Recurrent episodes of involuntary eating and drinking occurring during the main sleep period" is the primary criterion of SRED. This criterion does not mention clouded awareness or memory of eating and, in effect, incorporates NES into SRED. The critical issue of the relationship between the two disorders is ignored (*American Academy of Sleep Medicine. The International Classification of Sleep Disorders, 2nd ed: Diagnostic and coding manual. Westchester, IL: American Academy of Sleep Medicine; 2005; Vetrugno R et al, 2006; Stunkard AJ et al, 2009).* SRED probably represents a heterogeneous syndrome and it is currently still debated whether SRED and NES represent separate entities or simply two poles of a pathophysiologic continuum. Given the difficulties in the classification of SRED and/or NES and their relationship, this study will use the general term nocturnal eating disorders (NED).

3. Association of Restless Legs Syndrome with Nocturnal Eating Disorder.

A recent case-control study adopting validated criteria in a sufficiently large population showed a significant association between SRED and RLS, with a lifetime SRED prevalence of 33% in RLS patients and 1% in the control group (*Provini F et al, 2009*). An association between nocturnal eating and RLS had already been observed in an uncontrolled case series by Ekbom, whose first RLS description reported that RLS patients ‘‘could get up, walk, go into the kitchen and get something to eat’’ (*Ekbom KA, 1960*) and by Schenck et al. (*Schenck CH et al, 1993*) and Vetrugno et al. (*Vetrugno R et al, 2006*).

The nature of the association between SRED and RLS and its underlying mechanisms remain unclear. The eating behaviour could represent a sort of ‘‘killing time’’ behaviour performed in an attempt to recapture sleep, as already suggested (*Manni R et al, 1997*). Nocturnal eating more often (but not invariably) appeared after RLS onset, suggesting a pathophysiological mechanism related to the dopaminergic system, similar to RLS: beneficial effects of dopaminergic agents in SRED, association of nocturnal eating with increased motor activity (PLM, RMMA) and a demonstration of nocturnal eating/drinking syndrome secondary to neuroleptic-induced RLS (*Horiguchi J et al, 1999*), emphasized this hypothesis. On the other hand, drugs used to control RLS could be related to the onset of nocturnal eating, especially since amnestic SRED has been reported after zolpidem (*Morgenthaler TI and Silber MH, 2002*) and since benzodiazepines are recognized triggers for the onset of parasomnias. Furthermore, the patients often described the nocturnal eating episodes as occurring without hunger and associated with a feeling of being ‘‘out of control’’, in some way comparable to a compulsive behaviour. Interestingly, Provini et al’s study analysing the psychopathological profile of healthy subjects and RLS patients with and without nocturnal eating, showed that pathological values on the MOCI (Maudsley Obsessive Compulsive Inventory), a scale that specifically measures obsessive/compulsive characteristics, increased from controls to RLS patients without SRED to RLS with SRED. Conversely, no significant differences in demographics, habit features or clinical data, particularly RLS characteristics (including age at onset, positive family history, illness severity, medications for RLS symptoms), were found in the sample of RLS patients with SRED compared to RLS without SRED (*Provini F et al, 2009*).

Regarding psychiatric comorbidity and nocturnal eating in RLS, another study by the same group demonstrated an increased prevalence of current and lifetime nocturnal smoking (NS) in patients with RLS and in particular in RLS patients with nocturnal eating disorder *(Provini F et al, 2010*). Excessive smoking qualifies as a distinct psychiatric disturbance, with

affected patients displaying higher rates of anxiety and depression (*DSM IV, Diagnostic and Statistical Manual of Mental Disorders. IVth ed. American Psychiatric Association; 1994*). The same study also found that pathological obsessive-compulsive scores on the MOCI increased in RLS patients with NS, suggesting that NS in RLS could represent a compulsive habit behaviour possibly facilitated by the nocturnal arousals characteristic of RLS. Obviously, alternative explanations have not been excluded. Nicotine has some dopamine-stimulating effects (*Corrigall WA et al, 1994*), and nicotine intake during the night could ease the symptoms and signs of RLS. NS could also represent merely a way of killing time in an attempt to recapture sleep, since sleep fragmentation and wakefulness during the night are more likely to occur in RLS patients than in controls (*Provini F et al, 2010*).

An association with psychiatric disturbances, especially anxiety, depression and panic disorder have been reported in both RLS and NED (*Picchietti D and Winkelman JW, 2005; Winkelman JW et al, 2006; Lee HB et al, 2008; Howell MJ et al, 2009).* Higher scores for neuroticism and compulsivity were also reported in RLS patients (*Kalaydjian A et al, 2009; Scholz H et al, 2011*), although most studies explained the possible induction of compulsive behaviour in RLS by dopaminergic drugs, particularly DA agonists, emphasizing the role of dopaminergic mesolimbic stimulation in the reinforcement process of rewarding behavioural sequences (*Pourcher E et al, 2010*). Furthermore, self-perceived stress and sleep problems appear to distinguish compulsion-prone patients from the others (*Pourcher E et al, 2010*).

4. Objectives of the Study.

On the basis of the results of previous studies *(Provini F et al, 2009 and 2010)* we hypothesize that nocturnal eating behaviour may represent a real obsessive/compulsive trait in RLS, possibly related to dopaminergic mechanisms. In addition, the limbic system seems to be implicated in the pathophysiology of both RLS and obsessive-compulsive disorder *(Margariti*

PN et al, 2012; Rizzo G et al, 2012; Dichter GS et al, 2012). Therefore, the study aimed to evaluate psychiatric comorbidity in RLS patients without and with nocturnal eating disorder, untreated with dopamine agonists, analysing obsessive-compulsive traits together with mood and anxiety disorder, in comparison with a control group.

Furthermore, for the first time we investigated the two major domains of personality, temperament and character, in the three groups of subjects. According to Cloninger's biogenetic theory of personality, temperament refers to our congenital emotional predisposition. Temperament can be defined as the automatic associative response to emotional stimuli that determines habits and moods; it represents a trait of personality that is heritable, biologically and partly genetically determined, developmentally stable, uninfluenced by sociocultural learning, and regulated by limbic circuits connecting hippocampus, amygdala, hypothalamus, and related subcortical structures. On the other hand, character dimension is what people make of themselves intentionally, and refers to the self-awareness concepts that influence our voluntary intentions and attitudes. In contrast to temperament, character is weakly heritable, but is influenced by sociocultural learning. It matures in a stepwise manner in increments from infancy through late adulthood, and is regulated by the hippocampal formation and cerebral neocortex (*Cloninger CR, 1994*).

SUBJECTS AND METHODS

1. Subjects.

Patients with primary RLS (p-RLS) without nocturnal eating disorder (NED), and patients with p-RLS with NED were recruited by the Sleep Medicine Centre of the IRCCS, Institute of Neurological Sciences, and Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy. Healthy control subjects were recruited at the Psychiatry Unit of Parma Hospital.

Exclusion criteria were: 1) secondary forms of RLS; 2) neurological disease other than RLS; 3) serious and chronic medical diseases; 4) any psychiatric diagnosis, including major mood disorders (depressive illness or bipolar disorders), schizophrenia or other psychosis, bulimia nervosa and anorexia nervosa, or personality disorders; 5) previous head concussion; 6) dementia or mental retardation (IQ < 70); 7) drug or alcohol addiction; 8) any condition affecting the ability to complete the assessment, including low literacy or denial of informed consent.

Both patients and controls participated voluntarily in the study and gave their informed consent. The local institutional review board approved the project.

2. Procedure.

Each subject received two semi-structured interviews, each conducted by different researchers. The first interview was conducted by a neurologist expert in sleep medicine and consisted of three sections: the first collected demographic data and assessed general health status, (age, level of education, occupation, concomitant diseases, body mass index); the second assessed the presence/absence of the diagnostic criteria for p-RLS and for NED; the third examined RLS features (age at onset of RLS, positive family history of RLS, illness severity of RLS, RLS frequency in the last three months, daytime RLS symptoms, medication for RLS symptoms) and NED features (age at onset of NED, relationship between RLS and NED onset, NED frequency in the last three months).

Patients with p-RLS all met the revised criteria of IRLSSG (*Allen RP et al, 2003*). Secondary forms of RLS were excluded by exploring a detailed history, objective evaluation and using laboratory analyses such as haemoglobin, iron, ferritin, transferrin, creatinine, urea and liver enzymes, blood glucose, glycated haemoglobin. The severity of p-RLS was assessed using the IRLSSG rating scale (*Walters AS et al, 2003*).

In the absence of validated instruments specific for the investigation of NED, the questionnaire administered in the previous study was used (*Provini F et al, 2009*), including a list of items assembled in two sections: the first section comprised seven items being the Italian translation of the International Criteria for SRED (*American Academy of Sleep Medicine. The International Classification of Sleep Disorders, 2nd ed: Diagnostic and coding manual. Westchester, IL: American Academy of Sleep Medicine; 2005)*; the second section contained five items, a translation of the revised criteria for NES (*Birketvedt GS et al, 1999).* All p-RLS with NED met the criteria for SRED, two patients also those of NES.

The second interview was conducted by a psychiatrist: a first section was based on the Diagnostic and Statistical Manual of Mental Disorders 4th edition, revised text (DSM-IV-TR) (*American Psychiatric Association, 2000*) using the SCID-I-DSM-IV-TR (*First, Spitzer, Gibbon, & Williams, 2002*) and SCID-II-DSM-IV-TR (*First, Spitzer, Gibbon, Williams, & Benjamin, 1996*) to evaluate the presence of the psychiatric disorders considered exclusion criteria; a second section assessed family history of psychiatric disorder, anxiety disorders and depressive symptoms, compulsive-obsessive symptoms and personality traits (temperament and character). The self-administered and interviewer-administered questionnaires used were:

- *Hamilton Depression Rating Scale (HAM-D)* (*Hamilton M, 1960*; *Hedlund JL and Viewig BW, 1979*): also called the Hamilton Depression Rating Scale (HDRS), abbreviated HAM-D, is a 17-item clinician-rated scale used to provide an indication of depression, and as a guide to evaluate recovery (*Hamilton M, 1960).* The questionnaire is designed for adults and

is used to rate the severity of their depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms.

- ***Hamilton Anxiety Rating Scale (HAM-A)*** *(Hamilton, 1959):* the HAM-A is a 14-item clinician-rated scale used to measure prolonged state anxiety.

- ***State-Trait Anxiety Inventory (STAI)*** *(Spielberger CD et al, 1983)*: the STAI is divided into two sections, each having twenty questions, designed for measuring state anxiety, or anxiety about an event, and trait anxiety, that evaluated the frequency of how a person "generally feels" anxious. Respondents are asked to rate each item on a four-point Likert-type scale, ranging from 1 (almost never) to 4 (almost always). The total score ranges from 20 to 80, with higher scores indicating greater trait anxiety.

- ***Maudsley Obsessive Compulsive Inventory (MOCI)*** *(Hodgson RJ and Rachman S, 1977)* to measure obsessive-compulsiveness. The MOCI is a 30 true-false item scale designed to assess obsessive-compulsive symptoms. The scale measures four dimensions of obsessive-compulsive symptoms: checking compulsions, washing/cleaning compulsions, slowness, and doubting.

- ***Temperament and Character Inventory - revised (TCI)*** for analysis of personality traits: the TCI is a 240-item, self-administered, true/false questionnaire measuring seven personality dimensions based on Cloninger's psychobiological model of personality. This model claims that human personality is determined by temperament and character and assumes a seven-factor structure of personality (*Cloninger CR, 1994*). TCI includes four temperament dimensions (novelty seeking, harm avoidance, reward dependence and persistence) and three character dimensions (self-directedness, cooperativeness and self-transcendence). Novelty seeking is a tendency to respond actively to novel stimuli. It involves impulsiveness in decision-making. Harm avoidance is the tendency to respond intensely (behavioural inhibition) to signals of punishment or non-reward, and involves anticipatory worry on the possibility of problems, insecurity, and poor initiative. Reward dependence reflects an intense response to reward

and maintenance of rewarded behaviour. Individuals with high scores on reward dependence are described as sentimental, attached and easily influenced by others. Persistence represents the maintenance of behaviour in the face of frustration: it involves overachieving but also rigidity. Self-directedness expresses the ability to control, regulate, and adapt one's behaviour in order to achieve personal goals. Cooperativeness is the tendency to identify with and accept other individuals. It involves empathy, helpfulness and compassion. Self-transcendence expresses the degree of spiritual acceptance and identification with the wider world and also the acceptance of ambiguity and uncertainty. Items are rated on a five point Lickert's scale from "definitely false" (1) to "definitely true" (5).

3. Statistical Analysis.

Statistical differences in the main demographic, clinical, and psychometric variables were tested among the three groups (p-RLS without NED, p-RLS with NED and controls). χ^2 test was used for categorical variables. Kruskal-Wallis test, followed by Mann-Whitney U test for pair-wise comparisons, was used for ordinal variables. One-way ANOVA, followed by post-hoc LSD test for pair-wise comparisons, was used for continuous variables. Pearson's Correlation was used for correlation analysis. For all tests P values were considered significant if <0.05 after the application of the appropriate Bonferroni correction for multiple comparisons.

RESULTS

1. Subjects: Demographic and Clinical Data.

Ten patients with primary RLS (p-RLS) without nocturnal eating disorder (NED), ten patients with p-RLS with NED and ten healthy control subjects (age 52±6, mean ± SD; 53±11 and 52±10, respectively; all females. P=0.9) were recruited.

The characteristics of the ten p-RLS patients without NED, the ten p-RLS patients with NED and the ten controls are listed in **Table 1**. Age, level of education, occupation, concomitant diseases, and body mass index did not significantly differ among the three groups (all P>0.05).

The mean age (±SD) at onset of p-RLS was 39±14 years for p-RLS patients without NED and 42±16 for p-RLS patients with NED (P=0.7). Seven p-RLS patients without NED and four p-RLS patients with NED had a positive RLS family history (P=0.37). The mean (±SD) IRLSSG score was 17±10 and 19±13 in p-RLS patients without and with NED, respectively (P=0.8). In the last three months, nine patients with p-RLS without NED had RLS symptoms every day and one patient had symptoms two to three times/week. In the p-RLS with NED group, five patients had symptoms every day, four patients had symptoms two to five times/week and one patient had symptoms more rarely (2-3 times/year) (P=0.07).

Daytime RLS symptoms were present in seven and in five RLS patients without and with NED, respectively (P=0.65). No patient was being treated for symptoms of RLS during the period of interviews **(Table 1)**.

In the patients with p-RLS with NED the mean age (±SD) at onset of NED was 41±17 years. NED began one to 14 (mean 6) years after RLS onset in four patients, NED onset preceded RLS symptoms by eight to 17 (mean 10.6) years in three patients, two patients reported the concomitant onset of NED and RLS, while NED onset was unknown in one patient (**Table 2**).

In the last three months, two patients had nocturnal eating episodes every night, six patients had nocturnal eating episodes one to five times/week and two patients had nocturnal eating episodes one-two times/month. Nocturnal eating episodes could recur several times per night (**Table 2**).

2. Psychopathological Profile.

2.1 Family History of Psychiatric Disorder

Family history of psychiatric disorder did not significantly differ among the three groups (three p-RLS patients without NED, four p-RLS patients with NED and three controls had a positive family history of psychiatric disorder; P=0.86).

2.2 Depression and Anxiety Disorder

ANOVA test showed that the severity of depression scale resulting from the Hamilton-D did not differ (P=0.7) among the three groups of subjects, whereas the Hamilton-A scores significantly differed among the three groups (P=0.0002). Furthermore, a significant difference was evident for the STAI-Y Trait scores (P=0.043) but not for STAI-Y State scores (**Table 3**). Post-Hoc testing showed that the p-RLS patients without and with NED had significantly higher HAM-A (P=0.018 and P<0.0001, respectively) and STAI-Y Trait scores (P=0.028 and P=0.040, respectively) than controls. HAM-A and STAI-Y Trait scores did not significantly differ between p-RLS patients with and without NED (P=0.09 and P=1, respectively) (**Figure 4 and 5**). No correlation was found with RLS or NED clinical characteristics.

2.3 Maudsley Obsessive Compulsive Inventory

ANOVA test showed that the three groups had significantly different scores on MOCI scale total (P=0.004), doubting (P<0.0001) and checking compulsions (P=0.03) (**Table 4**). Post-hoc test showed that p-RLS patients with NED compared to controls had significantly higher MOCI scale total (P=0.002), doubting (P<0.0001) and checking compulsion (P=0.018) scores. In p-RLS patients without NED significantly higher doubting scores compared to controls (P=0.002) were found, whereas a trend towards higher MOCI-total scores and checking compulsion scores in comparison with controls was evident (P=0.06 and P=0.07, respectively). MOCI scale total

and checking compulsion scores of p-RLS patients with NED and without NED did not differ (P=0.45 and P=1, respectively). p-RLS patients with NED had significantly higher doubting scores (P=0.021) compared to p-RLS patients without NED (**Figure 6, 7 and 8**). No correlation was found with RLS or NED clinical characteristics.

2.4 Temperament and Character Inventory

Regarding temperament and character dimensions, ANOVA test showed that the groups differed in harm avoidance (HA) scores (P= 0.03). No difference was disclosed in the character dimensions (**Table 4**). Post-Hoc test showed that p-RLS patients with NED compared to controls had significantly higher HA scores (P=0.012). p-RLS patients without NED had HA scores intermediate between those of controls and those of p-RLS with NED, but without significant differences (P=0.28 and P=0.51, respectively) (**Figure 9**). No correlation was found with RLS or NED clinical characteristics.

DISCUSSION

We evaluated psychiatric comorbidity in p-RLS patients without and with nocturnal eating disorder, untreated with dopamine agonists, analysing obsessive-compulsive and personality traits together with mood and anxiety disorder, in comparison with a control group matched for age and sex.

Our study disclosed the following findings: i) p-RLS patients, particularly those with NED, have higher mean anxiety factor scores than controls; ii) MOCI-total score is significantly higher in p-RLS patients with NED and tends to be higher in those without NED compared to controls; iii) p-RLS patients with NED had significantly higher doubting and checking compulsion scores compared to controls, and significantly higher doubting scores compared to p-RLS patients without NED. p-RLS patients without NED had significantly higher doubting scores and a trend towards higher checking compulsion scores compared to controls; iv) p-RLS patients with NED had higher harm avoidance scores in the TCI scale compared to controls, whereas p-RLS patients without NED had intermediate HA scores but without significant differences compared to other groups.

We documented an association between RLS with/without NED and anxiety disorders confirming literature findings that higher mean anxiety/neuroticism factor scores were common in both RLS and NED syndrome (*Picchietti D and Winkelman JW, 2005; Winkelman JW et al, 2006; Lee HB et al, 2008; Kalaydjian A et al, 2009*; *Howell MJ et al, 2009*). The co-occurrence of RLS and mood and anxiety disorders remains a matter of debate: the sets of symptoms co-exist, high anxiety may be a predisposing factor for RLS, sleep deprivation inherent in RLS may enhance anxiety/neuroticism, and anxiety and RLS may result from a common CNS mechanism related to changes in central dopaminergic function. An association between a polymorphism in the dopamine transporter and anxiety/neuroticism (*Hunnerkopf R et al, 2007*) and correlations between striatal dopamine D2 receptor densities and anxiety/neuroticism scores (*Lee IH et al, 2005*) suggest an underlying biological component shared by the two disorder. Interestingly, our study found higher trait-anxiety rather than state-anxiety scores in p-RLS patients compared to controls.

We found a significantly higher MOCI-total score in p-RLS patients with NED and a trend towards higher MOCI-total score in p-RLS patients without NED compared to controls, with an apparent MOCI grading of severity from controls to p-RLS patients without NED to p-RLS with NED.

This is in agreement with a previous study (*Provini F et al, 2009*) showing, at post hoc analysis, that pathological values on the MOCI increased from controls to RLS patients without NED to RLS with NED (*Provini F et al, 2009*).

Furthermore, a similar grading of severity from controls to p-RLS patients without NED to p-RLS with NED for checking and especially doubting subscales was found analysing the subdimensions of the MOCI. Therefore, p-RLS patients and especially p-RLS patients with NED reported more obsessive-compulsive symptoms than controls. Accordingly, we hypothesize that NED represents a true obsessive/compulsive trait in RLS, possibly related to dopamine dysfunction.

Obsessive–compulsive disorder (OCD) is a condition where intrusive thoughts or images occur in patients' minds, provoking anxiety and stress, and where a specific behaviour is repeatedly performed to avoid these (*Cavedini P et al, 2006; Dichter GS et al, 2012*). Preclinical animal models and functional neuroimaging studies in patients with OCD have demonstrated a dysregulation in orbito-fronto-striatal inhibitory control pathways. Reward-pathway functions are mediated primarily by the ascending mesolimbic DA system that interdigitates with the limbic cortico-striatal-thalamic circuit in the process of reward information (*Haber SN, 2003*; *Chau DT et al, 2004; Dichter GS et al, 2012*). A reward circuitry dysfunction is implicated in compulsive behaviours, including food-seeking behaviour (*Blum K et al, 1995*). Interestingly, a dysfunction of the limbic system was also reported by imaging studies in RLS, in terms of dopaminergic receptor density (*Cervenka S et al, 2006),* metabolism (*Rizzo G et al, 2012),* and functional activation (*Margariti PN et al, 2012).*

To our knowledge, this is the first study to evaluate personality traits in RLS patients with and without NED. Cloninger's personality theory is based on a

biogenetic hypothesis of temperament and character underlying patterns of human behaviour. Temperament can be defined as a trait of personality that is heritable, biologically and partly genetically determined, developmentally stable, uninfluenced by sociocultural learning, and regulated by limbic circuits connecting hippocampus, amygdala, hypothalamus, and related subcortical structures. Character dimension is what people make of themselves intentionally, and in contrast to temperament, character is weakly heritable, but is influenced by sociocultural learning. It matures in a stepwise manner in increments from infancy through late adulthood, and is regulated by the hippocampal formation and cerebral neocortex (*Cloninger CR, 1994*).

Our study disclosed no significant differences among the three groups in the character dimensions of the TCI, but regarding the four dimensions of temperament, we detected higher harm avoidance (HA) scores in p-RLS patients with NED compared to the control group. HA is a trait of personality associated with higher sensitivity of the behavioural inhibition system and characterized by excessive worrying, pessimism, shyness, and being fearful, doubtful, and easily fatigued. HA refers to a heritable tendency to respond intensely to aversive stimuli and their conditioned signals, thereby facilitating learning to inhibit behaviour in order to avoid punishment, novelty, and frustrative omission of expected rewards (*Cloninger CR, 1987*). Higher HA scores have been found in patients with obsessive-compulsive disorder (*Bejerot S et al, 1998; Richter MA et al, 1996; Alonso P et al, 2008; Kim SJ et al, 2009*), and in their first degree relatives (*Ettelt et al., 2008*). HA has been associated with increased grey matter volume at the level of the left amygdala in female healthy subjects (*Iidaka et al., 2006*), and with different sex-related amygdala resting-state functional connectivity (*Li Y et al, 2012)*. Furthermore, HA has been associated with different patterns of limbic circuitry activation during risk-taking tasks (*Matthews SC et al, 2004; Paulus MP et al, 2003*).

Although multiple brain neurotransmitter systems are potentially involved in HA activity, Cloninger suggested that HA was correlated with high

serotonergic activity (*Cloninger CR, 1994*). However, some studies reported that dopaminergic neurotransmission may play a role in regulating neuronal activity associated with HA personality trait (*Yasuno F et al, 2001; Kim JH et al, 2011*), and, interestingly, higher HA scores were reported in disorders that may show symptoms of OCD (*Koo MS et al, 2010*), such as Tourette syndrome (*Horesh N et al, 2008*) and idiopathic Parkinson's disease (*Tomer R, Aharon-Peretz J, 2004*; *Kaasinen V et al, 2001*), whose pathophysiology is based on dopaminergic dysfunction.

Our study also found that p-RLS patients without NED had intermediate HA scores compared to other groups, with a grading of severity from controls to p-RLS patients without NED to p-RLS with NED similar to MOCI, although without significant differences probably due to the low number of subjects in each group.

Accordingly, higher levels of HA, a biologically determined personality trait, might constitute a diathesis predisposing individuals stimulated by sleep-related motor and autonomic arousal processes to display obsessive-compulsive symptoms, RLS and then, with increasing severity, compulsive nocturnal eating.

CONCLUSION

Our study disclosed the following findings: p-RLS patients, particularly those with NED, had increased anxiety factor scores; MOCI-total, doubting and checking compulsions, and TCI-HA scores were significantly higher in p-RLS patients with NED; p-RLS patients without NED had significantly higher MOCI-doubting scores and a trend towards higher checking compulsion and HA scores with an apparent grading from controls to p-RLS patients without NED to p-RLS with NED.

We speculate that higher levels of HA, a biologically determined personality trait, might constitute a diathesis predisposing individuals stimulated by sleep-related motor and autonomic arousal processes to display obsessive-compulsive symptoms, RLS and then, with increasing severity, compulsive nocturnal eating. In this scenario RLS and NED could represent a pathological continuum of a single disease entity in which a limbic system dysfunction, possibly driven by a dopaminergic impairment, could be the underlying pathophysiological mechanism. However, the low statistical power of this study precludes a definitive conclusion. We cannot exclude that NED may simply be an RLS co-morbidity or that the eating behaviour is a sort of ‘‘killing time’’ activity performed in an attempt to recapture sleep. In both cases NED seems to occur more readily in biologically predisposed individuals, for example those with a particular temperament trait such as higher HA scores.

The relationship between psychiatric comorbidity and nocturnal eating in RLS warrants further investigation, especially in prospective studies, and obsessive-compulsive symptoms should be analyzed together with personality traits.

TABLES AND FIGURES

Table 1. Clinical and socio-demographic variables of p-RLS patients with NED, p-RLS patients without NED, and controls. No difference was found among the three groups (all P>0.05).

	p-RLS patients with NED	p-RLS patients without NED	Control Group
Age (yrs) mean ± SD	**53±11**	**52±6**	**52±10**
Men	/	/	/
Women	**10**	**10**	**10**
Level of education			
middle school	**5**	**4**	**4**
upper secondary school	**5**	**6**	**6**
Occupation			
Employed	**7**	**4**	**4**
Housewife		**3**	**1**
Professional		**2**	**2**
Retired	**3**	**1**	**1**
Unemployed			**2**
Body mass index mean (±SD)	**26±4**	**27±5**	**25±6**
Concomitant diseases	**7**	**5**	**5**
Systemic hypertension	***5***	***2***	**3**
Thyroid pathologies	***2***	***3***	**2**
Age at onset of p-RLS (mean ± SD)	**42±16**	**39±14**	/
Positive family history	**4**	**7**	/
RLS Severity (mean ± SD)	**19±13**	**17±10**	/
RLS frequency (in the last three months)			
2-3 times/week	**2**	**1**	
4-5 times/week	**2**		
6-7 times/week	**5**	**9**	
1-2 times/month			
3-4 times/month			
2-3 times/year	**1**		
Daytime p-RLS symptoms	**5**	**7**	/
Medication for p-RLS symptoms	**Drug-free**	**Drug-free**	/

p-RLS= Primary Restless Legs Syndrome; NED= Nocturnal Eating Disorder

Table 2. Clinical features of NED in p-RLS patients.

	p-RLS patients with NED (Number)
NED onset	
NED onset after p-RLS	**4**
NED onset before p-RLS	**3**
NED onset concomitant with p-RLS	**2**
Unknown	**1**
NED frequency (in the last three month)	
every night	**2**
3-5 times/week	**5**
1-2 times/week	**1**
1-2 times/month	**2**
1-6 times/year	
Number of eating episodes per night	
1-2 episodes/night	**8**
3-5 episodes/night	**2**

p-RLS= Primary Restless Legs Syndrome; NED= Nocturnal Eating Disorder

Table 3. Different scores (mean ± standard deviation) on Depression and Anxiety Scales in the three groups studied.

	Controls	p-RLS patients without NED	p-RLS patients with NED	P (ANOVA)*
HAMILTON-D	4.7±2.1	6.9±6.5	9.1±7.4	0.7
HAMILTON-A	4.7±3.0	14.3±8.4	21.6±8.6	***0.0002***
STAI-Y State score	31.1±9.5	43.8±14.3	40.4±12.3	0.21
STAI-Y Trait score	32.5±10.9	47.2±13.4	46.4±10.5	***0.043***

p-RLS= Primary Restless Legs Syndrome; NED= Nocturnal Eating Disorder; HAMILTON-D= Hamilton scale for Depression; HAMILTON-A= Hamilton scale for Anxiety; STAI-Y= State-Trait Anxiety Inventory – Trait and State version.

* Corrected for multiple comparisons

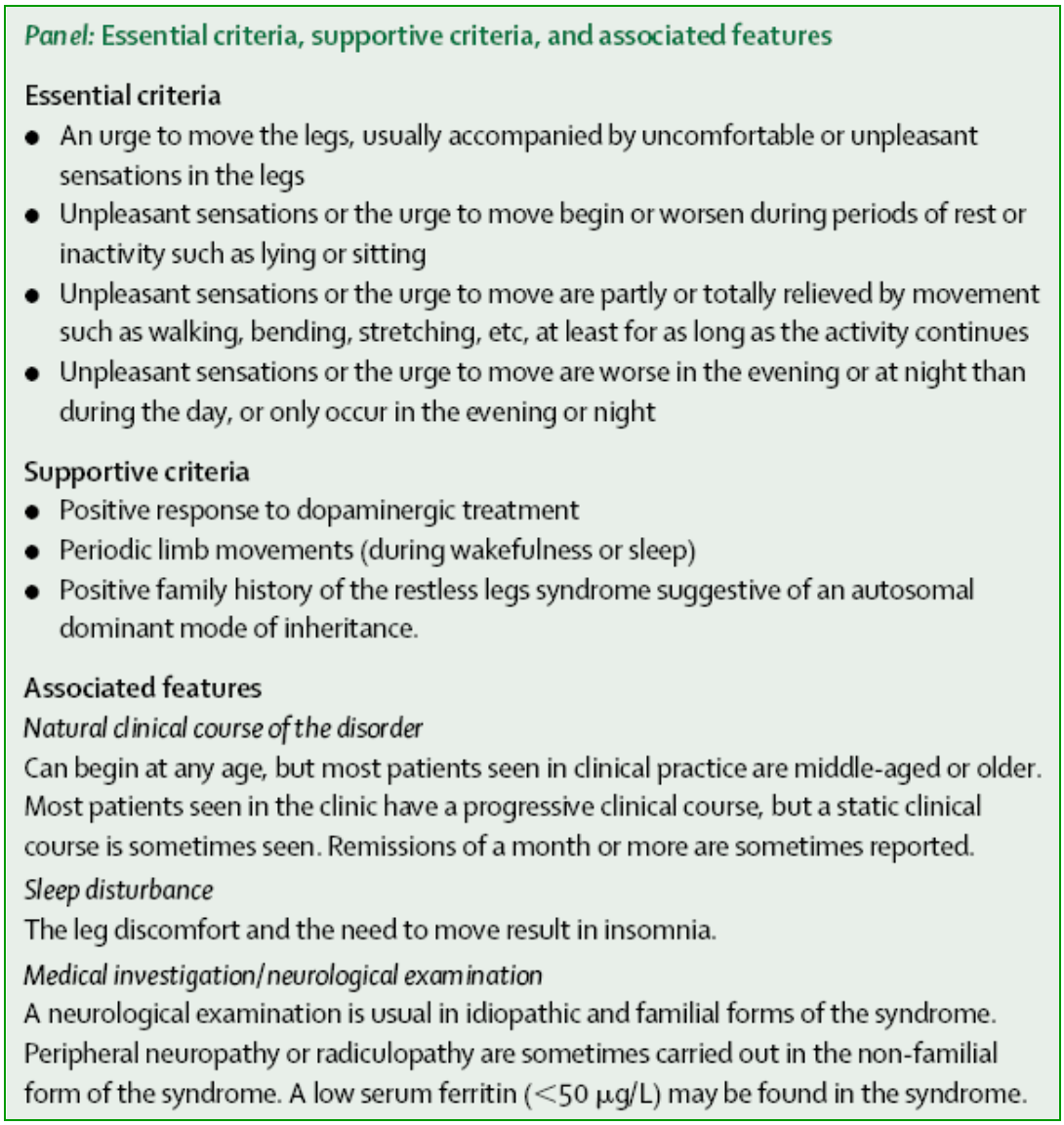
Table 4. Different scores (mean ± standard deviation) on the Maudsley Obsessive Compulsive Inventory (MOCI) and Temperament and Character Inventory (TCI) in the three groups studied.

		Controls	p-RLS patients without NED	p-RLS patients with NED	P (ANOVA)*
MOCI-Total		8±2.6	12.2±5	14.7±3.2	**0.004**
MOCI- checking		7.7±13.7	28.6±24.4	34.1±19.7	**0.03**
MOCI- cleaning		37.8±13.2	41.4±18.1	42.3±12.7	1
MOCI- slowness		33.6±7.2	28±16.1	30.9±13	1
MOCI- doubting		9.8±13.2	42.4±22.3	66.7±19.2	**<0.0001**
TCI	TCI-HA	15.6±4.3	20.3±8.1	24.1±4.9	**0.03**
	TCI-NS	21.4±5	19.3±7.5	15.7±9.4	0.5
	TCI-RD	15.4±2.6	14.3±3.3	13.6±4.5	1
	TCI-P	3.8±1.1	4.4±1.5	4.9±2.1	0.7
	TCI-SD	30.8±2.9	26.4±7.9	26.2±7.5	0.45
	TCI-C	34.7±3.5	30.5±4.3	30.8±5.5	0.18
	TCI-ST	21.9±2.1	20.8±2.1	20.5±3.1	0.85

p-RLS= Primary Restless Legs Syndrome; NED= Nocturnal Eating Disorder; MOCI= Maudsley Obsessive-Compulsive Inventory; TCI= Temperament and Character Inventory; HA= Harm Avoidance; NS= Novelty Seeking; RD= Reward Dependence; P= Persistence; SD= Self-Directedness; C= Cooperativeness; ST= Self-Transcendence.

* Corrected for multiple comparisons

Figure 1. Diagnostic Criteria of Restless Legs Syndrome



Panel: Essential criteria, supportive criteria, and associated features

Essential criteria

- An urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations in the legs
- Unpleasant sensations or the urge to move begin or worsen during periods of rest or inactivity such as lying or sitting
- Unpleasant sensations or the urge to move are partly or totally relieved by movement such as walking, bending, stretching, etc, at least for as long as the activity continues
- Unpleasant sensations or the urge to move are worse in the evening or at night than during the day, or only occur in the evening or night

Supportive criteria

- Positive response to dopaminergic treatment
- Periodic limb movements (during wakefulness or sleep)
- Positive family history of the restless legs syndrome suggestive of an autosomal dominant mode of inheritance.

Associated features

Natural clinical course of the disorder

Can begin at any age, but most patients seen in clinical practice are middle-aged or older. Most patients seen in the clinic have a progressive clinical course, but a static clinical course is sometimes seen. Remissions of a month or more are sometimes reported.

Sleep disturbance

The leg discomfort and the need to move result in insomnia.

Medical investigation/neurological examination

A neurological examination is usual in idiopathic and familial forms of the syndrome. Peripheral neuropathy or radiculopathy are sometimes carried out in the non-familial form of the syndrome. A low serum ferritin (<50 μg/L) may be found in the syndrome.

International Restless Legs Syndrome Study Group, 1995; Allen RP et al, 2003

Figure 2. Diagnostic Criteria of Sleep-Related Eating Disorder

A. Recurrent episodes of involuntary eating and drinking occur during the main sleep period.

B. One or more of the following must be present with the recurrent episodes of involuntary eating and drinking:

1. Consumption of peculiar forms or combinations of food or inedible or toxic substances.
2. Insomnia related to sleep disruption from repeated episodes of eating, with a complaint non restorative sleep, daytime fatigue, or somnolence.
3. Sleep-related injury.
4. Dangerous behaviors performed while in pursuit of food or while cooking food
5. Morning anorexia.
6. Adverse health consequences from recurrent binge eating of high caloric food.

C. The disturbance is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use or substance use disorder (hypoglycemic states, peptic ulcer disease, reflux esophagitis, Kleine-Levin syndrome, Kluver-Bucy syndrome, and nighttime extension of daytime Anorexia Nervosa (binge/purge subtype), bulimia nervosa, and binge eating disorder).

[a]From The International Classification of Sleep Disorders: Diagnostic and Coding Manual, 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005:174-5.

Figure 3. Diagnostic Criteria of Night Eating Disorder (NES)

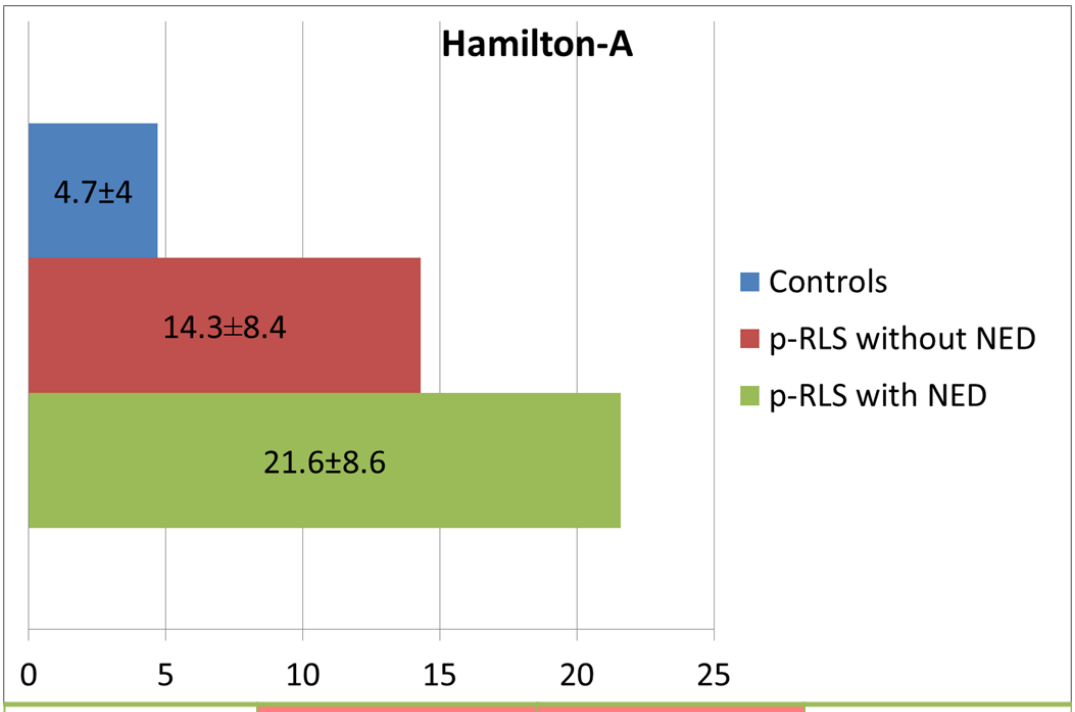
Evening hyperphagia
Nocturnal awakenings
Nocturnal hyperphagia
Morning anorexia
Absence of other eating disorders behaviour

From Birketvedt GS et al, 1999

A. The daily pattern of eating demonstrates a significantly increased intake in the evening and/or nighttime, as manifested by one or both of the following:
   1. At least 25% of food intake is consumed after the evening meal
   2. At least two episodes of nocturnal eating per week
B. Awareness and recall of evening and nocturnal eating episodes are present.
C. The clinical picture is characterized by at least three of the following features:
   1. Lack of desire to eat in the morning and/or breakfast is omitted on four or more mornings per week
   2. Presence of a strong urge to eat between dinner and sleep onset and/or during the night
   3. Sleep onset and/or sleep maintenance insomnia are present four or more nights per week
   4. Presence of a belief that one must eat in order to initiate or return to sleep
   5. Mood is frequently depressed and/or mood worsens in the evening
D. The disorder is associated with significant distress and/or impairment in functioning.
E. The disordered pattern of eating has been maintained for at least 3 months.
F. The disorder is not secondary to substance abuse or dependence, medical disorder, medication, or another psychiatric disorder.

From Allison CK et al, 2010

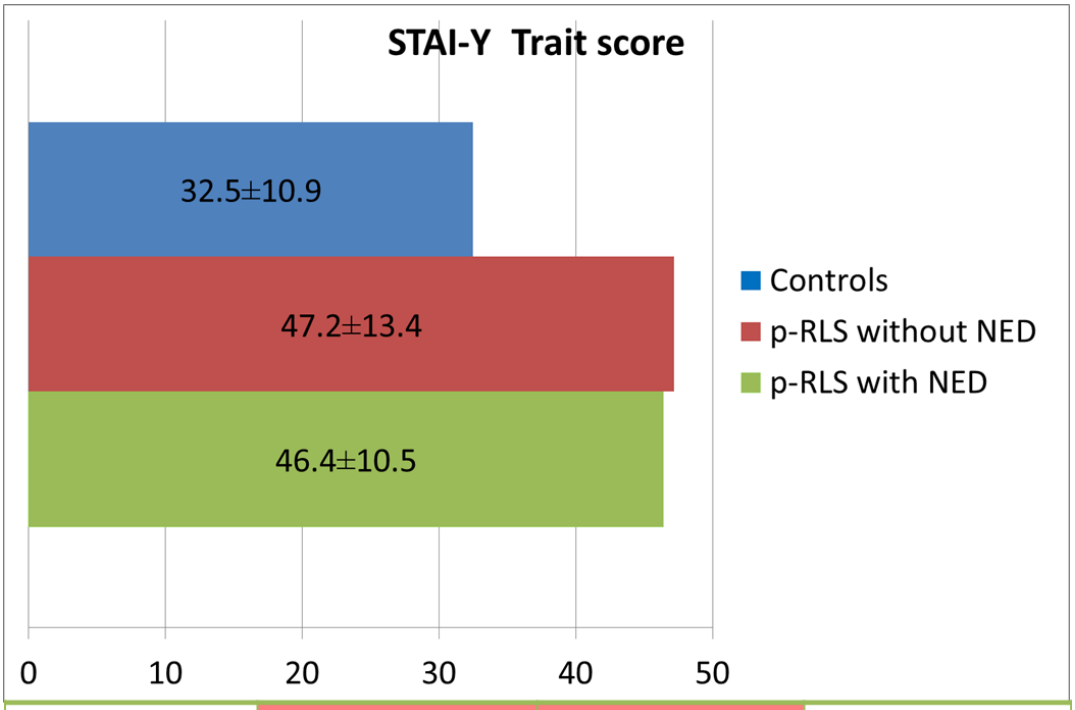
Figure 4. Post-hoc test (LSD test followed by Bonferroni correction) for HAMILTON-A= Hamilton Scale for Anxiety.



	p-RLS without NED *vs* Controls	p-RLS with NED *vs* Controls	p-RLS with NED *vs* p-RLS without NED
P (BONFERRONI)	***P=0.018***	***P<0.0001***	*P=0.09*

p-RLS= Primary Restless Legs Syndrome; NED= Nocturnal Eating Disorder.

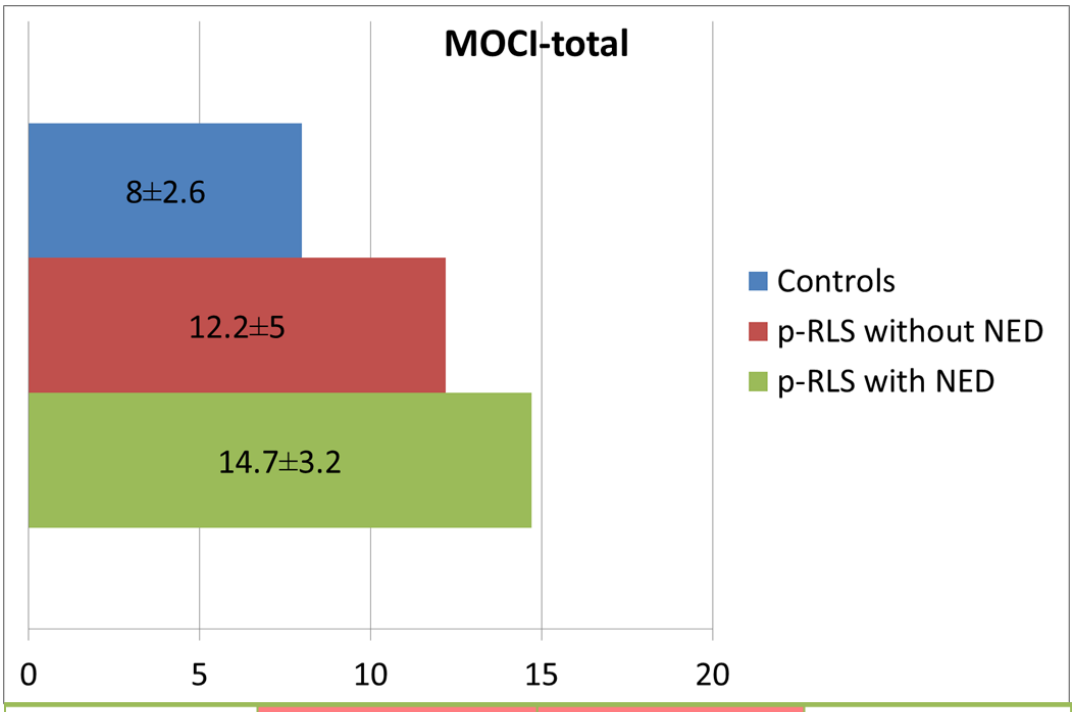
Figure 5. Post-hoc test (LSD test followed by Bonferroni correction) for STAI-Y= State-Trait Anxiety Inventory – Trait version.



	p-RLS without NED *vs* Controls	p-RLS with NED *vs* Controls	p-RLS with NED *vs* p-RLS without NED
P (BONFERRONI)	***P=0.028***	***P=0.040***	*P=1*

p-RLS= Primary Restless Legs Syndrome; NED= Nocturnal Eating Disorder.

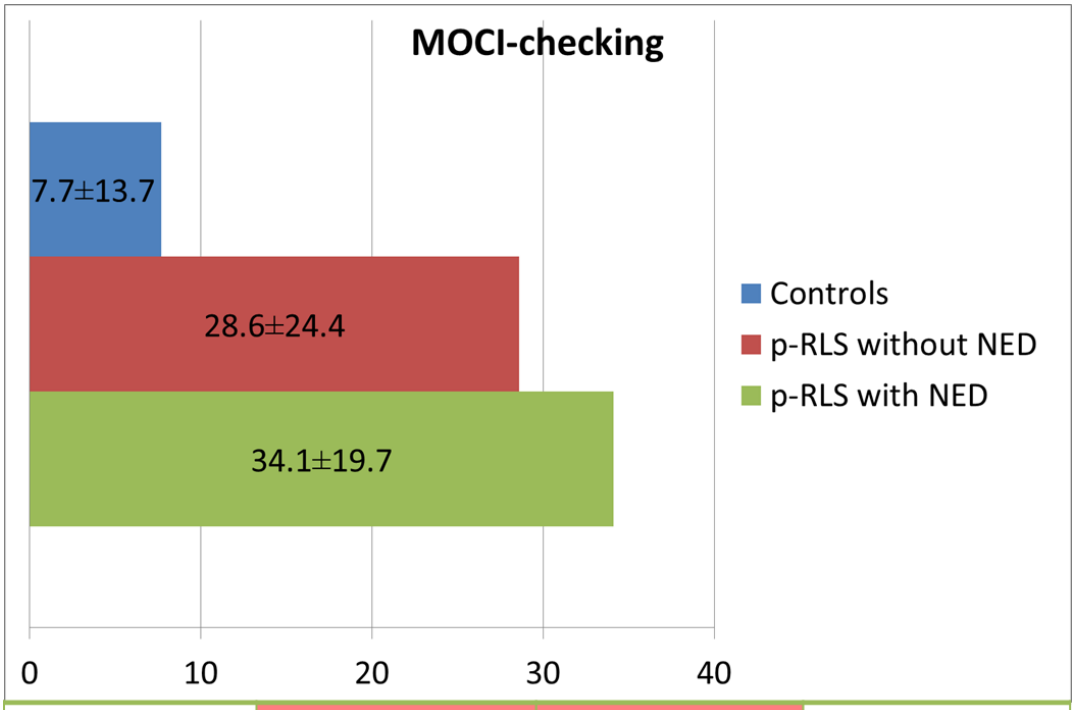
Figure 6. Post Hoc test (LSD test followed by Bonferroni correction) for Maudsley Obsessive-Compulsive Inventory (MOCI) total scores.



	p-RLS without NED *vs* Controls	p-RLS with NED *vs* Controls	p-RLS with NED *vs* p-RLS without NED
P (BONFERRONI)	***P=0.06***	***P=0.002***	*P=0.45*

p-RLS= Primary Restless Legs Syndrome; NED= Nocturnal Eating Disorder.

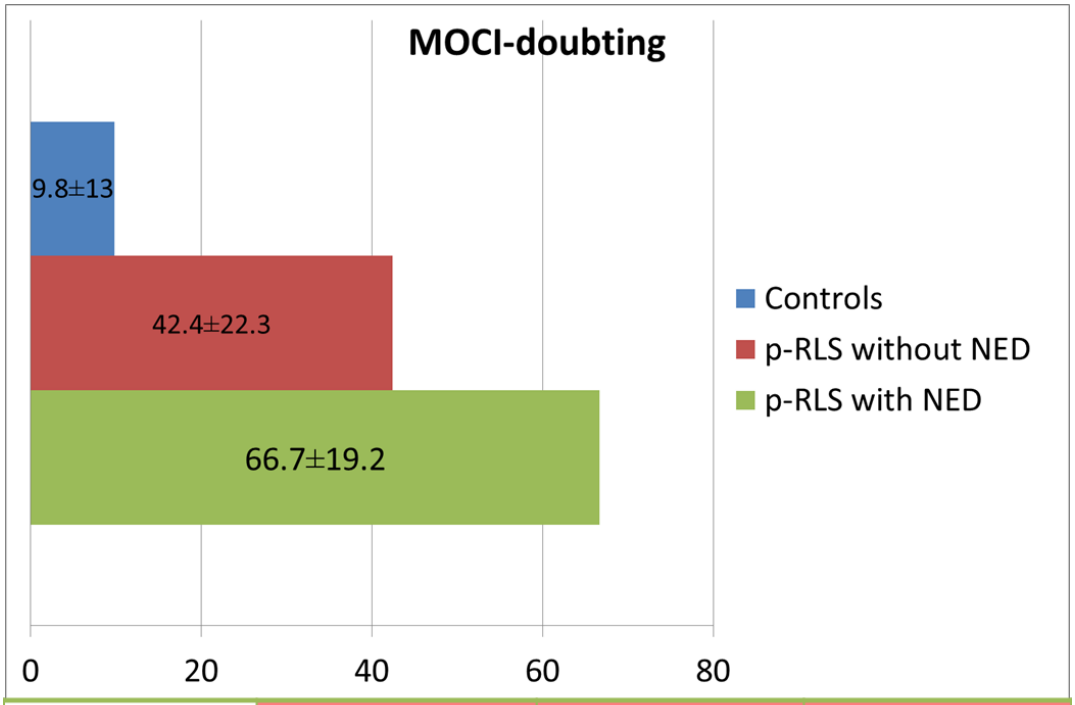
Figure 7. Post Hoc test (LSD test followed by Bonferroni correction) for Maudsley Obsessive-Compulsive Inventory (MOCI)-checking scores.



	p-RLS without NED *vs* Controls	p-RLS with NED *vs* Controls	p-RLS with NED *vs* p-RLS without NED
P (BONFERRONI)	*P=0.07*	*P=0.018*	*P=1*

p-RLS= Primary Restless Legs Syndrome; NED= Nocturnal Eating Disorder.

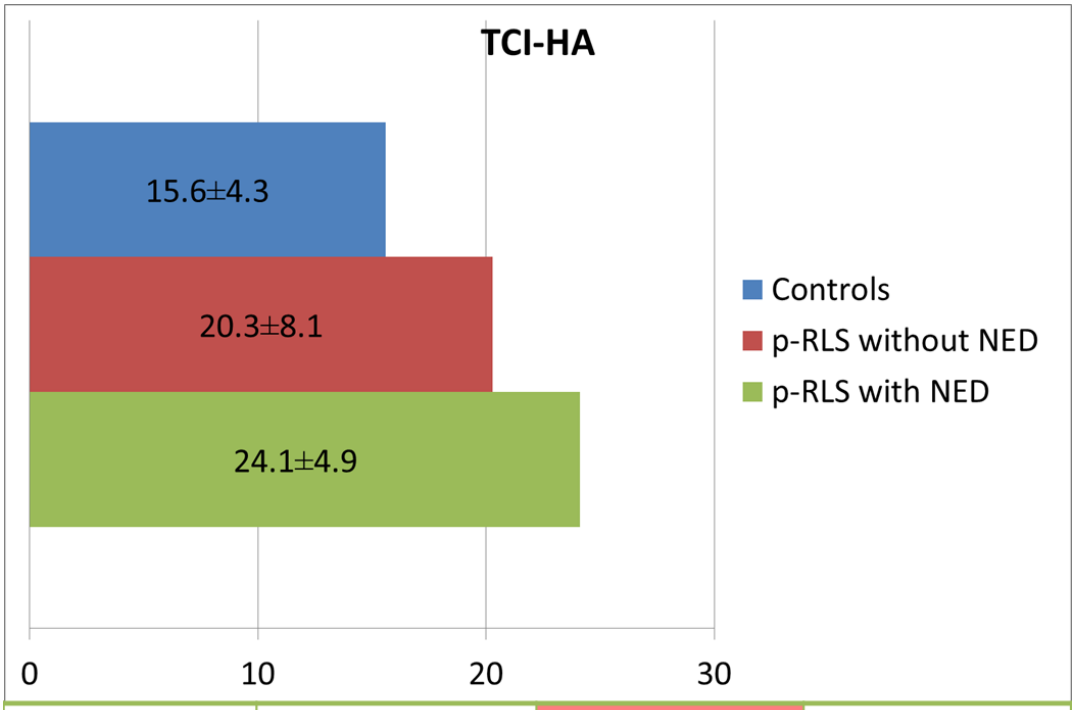
Figure 8. Post Hoc test (LSD test followed by Bonferroni correction) for Maudsley Obsessive-Compulsive Inventory (MOCI)-doubting scores.



	p-RLS without NED *vs* Controls	p-RLS with NED *vs* Controls	p-RLS with NED *vs* p-RLS without NED
P (BONFERRONI)	*P=0.002*	*P<0.0001*	*P=0.021*

p-RLS= Primary Restless Legs Syndrome; NED= Nocturnal Eating Disorder.

Figure 9. Post Hoc test (LSD test followed by Bonferroni correction) for Temperament and Character Inventory (TCI)-Harm Avoidance scores.



	p-RLS without NED *vs* Controls	p-RLS with NED *vs* Controls	p-RLS with NED *vs* p-RLS without NED
P (BONFERRONI)	*P=0.28*	***P=0.012***	*P=0.51*

p-RLS= Primary Restless Legs Syndrome; NED= Nocturnal Eating Disorder.

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